Pharmacovigilance of Veterinary Medicinal Products
Management of adverse event reports

I. Introduction

Pharmacovigilance of veterinary medicinal products (VMPs) can be defined as the detection and investigation of the effects of the use of these products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products. This document will only deal with the spontaneous reporting system for identification of possible adverse events following the use of marketed VMPs.

Within all regions involved in the VICH process there are certain legal obligations for the pharmaceutical industry, the commercial party responsible for the products, with regard to adverse events reported to them. Those legal obligations relate to the acceptance of adverse event reports and the storage and submission of those reports to the authorities.

It is of importance for all parties, the Marketing Authorization Holders (MAHs), the Regulatory Authorities and the users of VMPs to develop harmonized and common systems, common definitions and standardized terminology within pharmacovigilance. Harmonization of those elements between the regions facilitates the reporting responsibilities for the MAHs, many with worldwide activities. At the same time harmonization of systems and requirements facilitates the inter-regional comparison of data and exchange of information, thereby increasing the general knowledge of a product`s general performance and safety profile.

II. Scope

The scope of pharmacovigilance in this VICH document is the management of the detection and investigation of the clinical effects of marketed VMPs mainly concerned with the safety and efficacy in animals and the safety in people exposed to these products. While pharmacovigilance in its broadest sense may entail a wide range of activities, this document only deals with the spontaneous reporting system for the identification of possible adverse events following the use of marketed VMPs.

III. Definitions

The terms and definitions in this document are intended to harmonize other previously used terms referring to similar concepts. Within the scope of this document the following definitions of items or actions have been developed.

III.1 Veterinary Medicinal Product (VMP)

Any medicinal product with approved claim(s) to having a protective, therapeutic or diagnostic effect or to alter physiological functions when administered to or applied to an animal. The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function.

III.2 Adverse event (AE)

An adverse event is any observation in animals, whether or not considered to be product-related, that is unfavorable and unintended and that occurs after any use of VMP (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy or noxious reactions in humans after being exposed to VMP(s).

III.3 Serious adverse event

A serious adverse event is any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event.

III.4 Unexpected adverse event

An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labeling or approved documents describing expected adverse events for a VMP.

III.5 Adverse Event Report (AER)

An adverse event report is a direct communication from an identifiable first-hand reporter that includes at least the following information:

- an identifiable reporter
- an identifiable animal(s) or human
- an identifiable VMP
- one or more adverse events

III.6 Marketing Authorization Holder (MAH)

The Marketing Authorization Holder is the commercial party who, according to the national or regional regulations, is legally responsible for the pharmacovigilance of the VMP.

III.7 Regulatory Authority (RA)

The Regulatory Authority is the national or regional authority which, according to the legislation, is responsible for the issuing, adaptation or withdrawal of marketing authorizations/licences of VMPs and for pharmacovigilance activities.

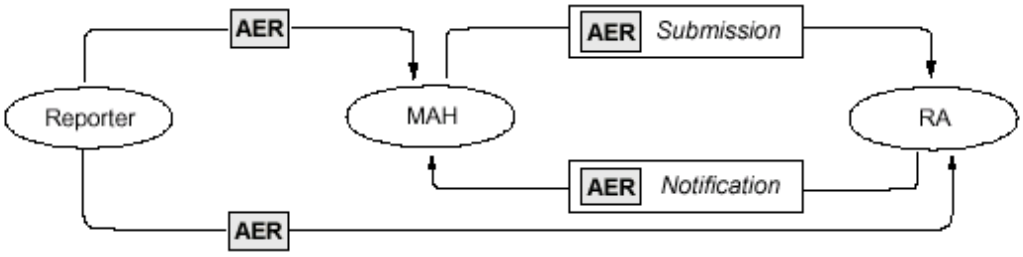
III.8 Periodic Summary Update (PSU)

The document submitted to the RA at set intervals to support the continued marketing and the adequacy of the approved labeling of the VMP. This document will include an analysis of all AERs received during the interval and may include a bibliographical listing of articles published that pertain to the safety or efficacy of the VMP. The analysis will include a summary and review of the type, severity, and frequency of the AERs received related to the quantity sold, and a review of resulting actions.

IV. The Pharmacovigilance Process

IV.1 Information flow in the Pharmacovigilance System.

The flow of information is illustrated below:



Information flow in the pharmacovigilance system.
Data preferably flows as shown in the upper half of the figure, where the reporter communicates with the MAH and the MAH submits AERs it has received to the RA. An alternate path is shown in the lower half, where the reporter communicates with the RA and the RA notifies the MAH of AERs it has received.

IV.2 Informational unit

The basic unit of information in the pharmacovigilance system covered by this document is the AER.

IV.3 Recording AERs

The MAH must record each AER received and store it in a manner which allows easy access to the data. The receipt, acknowledgement or recording of an AER by the MAH or the RA does not necessarily have any implication regarding the veracity or authenticity of the AER nor implies any degree of causality.

IV.4 Submitting AERs

The MAH submits an AER to the regional RA where the adverse event purportedly occurred as provided by the relevant requirements, either as an expedited submission or as

a periodic submission. The submission of an AER does not necessarily imply an endorsement or agreement with its content, unless regional or national regulations require differently.

IV.5 Expedited AER submissions

The expedited submission of certain AERs may be required, related to the seriousness or unexpectedness of the reported event or because of the urgency of its implications regarding the safety of animals or man. If, based on these expedited submissions, the regional RA decides on a regulatory action, the MAH should immediately inform all relevant regional RAs about this action.

IV.6 Periodic AER submissions

At regular intervals, the MAH should submit all AERs not previously submitted.

IV.7 Reporting source

Although reporting via the attending veterinarian is encouraged, an AER may be initiated by anyone directly involved with the purported adverse event. Preferably, an AER is communicated by the reporter directly to the MAH, but the AER may also have been routed through an agent. A communication through an intermediate agent is considered an AER only if the agent has been authorized by the reporter and provides sufficient information to allow direct contact between the reporter and the MAH.

V. Data elements for the transmission of adverse event reports

The format for submitting information about an AER includes provisions for transmitting all the relevant data elements useful to assess an AER. The data elements are sufficiently comprehensive to cover complex reports from most sources, different sets, and transmission situations or requirements. In many, if not most, instances a substantial number of data elements will not be known.

Data elements, as defined in this document, are requied for electronic transmission. Other items necessary for electronic submission are:

- controlled vocabularies
- relationships between data elements
- procedures for electronic submission

These items will be addressed in the future.

The specific data elements are described as follows:

A. Administrative and identification information

A.1 Regulatory Authority

Business name
Street address
City
State/county
Mail/zip code
Country

User guidance:
RA where the AER is sent.

NOTE CONCERNING TRANSMISSION:
TEXT

A.2 Marketing Authorisation Holder

A.2.1 MAH information

Business name
Street address
City
State/county
Mail/zip code
Country

A.2.2 Person acting on behalf of MAH

Title
First name
Last name
Telephone
Fax
e-mail

User guidance:
The person acting on behalf of the MAH is the contact person for this AER and its contents.

NOTE CONCERNING TRANSMISSION:
TEXT

A.3 Persons involved in the AER

A.3.1 Attending veterinarian

Title
First name
Last name Business name
Street address
City
State/county
Mail/zip code
Country
Telephone
Fax
e-mail

User guidance:
Veterinarian or other health professional.

NOTE CONCERNING TRANSMISSION:
TEXT

A.3.2 Animal owner

Same as in A.3.1.

User guidance:
Animal owner or tender of the animal(s).

NOTE CONCERNING TRANSMISSION:
TEXT

A.3.3 Primary reporter category

User guidance:
The individual/organization providing the primary information for the AER.

NOTE CONCERNING TRANSMISSION:
LIST: VETERINARIAN, ANIMAL OWNER, PHYSICIAN, PATIENT, OTHER HEALTH PROFESSIONALS, UNKNOWN

A.4 AER information

A.4.1 AER identification number

User guidance:
Unique identifier for the AER, designated by the MAH, to be referred to in future follow-ups.

NOTE CONCERNING TRANSMISSION:
TEXT

A.4.2 AER submission status

NOTE CONCERNING TRANSMISSION:
LIST: INITIAL, FOLLOW-UP

A.4.3 Date received by MAH

User guidance:
Date initial AER received.

NOTE CONCERNING TRANSMISSION:
DATE FORMAT: DAY, MONTH, YEAR

A.4.4 Date of submission

User guidance:
Date current AER submitted to RA.

NOTE CONCERNING TRANSMISSION:
DATE FORMAT: DAY, MONTH, YEAR

A.4.5 Type of submission

NOTE CONCERNING TRANSMISSION:
LIST: EXPEDITED, PERIODIC

B. Description of the AE

B.1 Animal data

User guidance:
Except for B.1.1, data relates to the affected animals only.

B.1.1 Number of animals exposed

User guidance:
(Estimated) number of animals exposed/treated.

NOTE CONCERNING TRANSMISSION:
INTEGER

B.1.2 Number of animals affected

User guidance:
(Estimated) number of animals affected in the AER.

NOTE CONCERNING TRANSMISSION:
INTEGER

B.1.3 Species

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.1.4 Breed

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.1.5 Production type

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.1.6 Sex

NOTE CONCERNING TRANSMISSION:
LIST: FEMALE, MALE, UNKNOWN

B.1.7 Physiological status

NOTE CONCERNING TRANSMISSION:
LIST: INTACT, NEUTERED, PREGNANT, UNKNOWN

B.1.8 Weight

User guidance:
(Estimated) weight in kilos of the animal(s) affected.

NOTE CONCERNING TRANSMISSION:
NUMBER (2 DECIMALS)

B.1.9 Age

User guidance:
(Estimated) age of the animal(s) affected.

NOTE CONCERNING TRANSMISSION:
NUMBER (2 DECIMALS) AND UNITS (MINUTES, HOURS, DAYS, WEEKS, MONTHS, YEARS, UNKNOWN)

B.1.10 State of health at time of exposure

NOTE CONCERNING TRANSMISSION:
LIST: GOOD, FAIR, POOR, UNKNOWN

B.1.11 Illness/reason for use of VMP(s)

User guidance:
The actual reason for use should be noted, not by default the registered indication(s). Mention symptoms if informative.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2 VMP(s) data and usage

User guidance:
The information below should be given for all VMP(s) involved in the AE.

B.2.1 Brand name

User guidance:
Brand name of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.2 Registration number

User guidance:
Registration number of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.3 Active ingredient

User guidance:
Active ingredient of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.4 Strength

User guidance:
Concentration of the active ingredient of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.5 Dosage form

User guidance:
Dosage form of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.2.6 Company

User guidance:
Company involved with the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.7 Lot number

User guidance:
Lot number of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.8 Route of exposure

User guidance:
Route of exposure/administration of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.2.9 Dose per administration

User guidance:
Real dose administered, not by default the dosage as registered.

NOTE CONCERNING TRANSMISSION:
TEXT

B.2.10 Interval of administration

User guidance:
Interval of administration or frequency or administration of the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.2.11 Date of first exposure

User guidance:
(Approximate) date of first exposure/treatment with VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
DATE FORMAT: DAY, MONTH, YEAR

B.2.12 Date of last exposure

User guidance:
(Approximate) date of last exposure/treatment with VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
DATE FORMAT: DAY, MONTH, YEAR

B.2.13 Who administered the VMP

User guidance:
Category of the person who administered the VMP involved in the AE.

NOTE CONCERNING TRANSMISSION:
LIST: VETERINARIAN, OWNER, MEDICAL STAFF, OTHER, UNKNOWN

B.2.14 Use according to label

User guidance:
Information on whether the VMP was used according to its label recommendations.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN

B.2.15 Explanation for off-label use

User guidance:
Explanation on why the VMP was not used according to its label recommendations. To be filled only if 'no' was selected in B.2.14.

NOTE CONCERNING TRANSMISSION:
TEXT

B.3 Adverse event data

B.3.1 Date of onset of AE

User guidance:
(Approximate) date on onset of the AE.

NOTE CONCERNING TRANSMISSION:
DATE FORMAT: DAY, MONTH, YEAR

B.3.2 Length of time between exposure to primarily suspect VMP(s) and onset of AE

User guidance:
Primarily suspect VMP(s) are those VMP(s) for which the submitting MAH is responsible. Length of time refers to the difference between B.2.12 and B.3.1.

NOTE CONCERNING TRANSMISSION:
LIST OF BIOLOGICALLY RELEVANT CATEGORIES (TO BE DETERMINED)

B.3.3 Duration of AE

User guidance:
(Approximate) length of time the AE lasted.

NOTE CONCERNING TRANSMISSION:
TEXT

B.3.4 Narrative of AE

User guidance:
Describe the sequence of events including:
- *administration of VMP(s)*
- *all clinical signs*
- *sites of reaction*
- *severity*
- *pertinent laboratory test results*
- *necropsy results*
- *possible contributing factors*
- *treatment of AE*

- *relevant medical history*

NOTE CONCERNING TRANSMISSION:
TEXT

B.3.5 Adverse clinical manifestations

User guidance:
Adverse clinical manifestations observed in the AE.

NOTE CONCERNING TRANSMISSION:
LIST (TO BE DETERMINED)

B.3.6 Treatment of AE

User guidance:
If the AE was treated, description of the treatment should be done in the narrative B.3.4.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN

B.3.7 Relevant medical history

User guidance:
If there is relevant medical history for the affected animal(s) which will help the assessment of the AE, include it in the narrative B.3.4.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN

B.3.8 Outcome to date

B.3.8.1 Ongoing
B.3.8.2 Recovered
B.3.8.3 Alive with sequelae
B.3.8.4 Died
B.3.8.5 Killed/euthanized
B.3.8.6 Unknown

User guidance:
The number of animal(s) in each category should be given. Sequelae mean irreversible effects. The total number from B.3.8.1 to B.3.8.6 should be equal to B.1.2.

NOTE CONCERNING TRANSMISSION:
LIST: INTEGER

B.4 Dechallenge-Rechallenge information

User guidance:
The information in that section relates to affected animal(s).

B.4.1 Previous exposure to the primarily suspect VMP(s)

User guidance:
Only exposures outside the dates mentioned in B.2.11 and B.2.12. If yes is selected, put the dates of previous exposure in the narrative B.3.4.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN

B.4.2 Previous AE to the primarily suspect VMP(s)

User guidance:
Only clinical manifestations outside those mentioned in B.3.5. If yes is selected, put the clinical signs in the narrative B.3.4.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN

B.4.3 Did AE abate after stopping the primarily suspect VMP(s)

User guidance:
'Not applicable' is used when there is no repeated dose or long-lasting signs.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN, NOT APPLICABLE

B.4.4 Did AE reappear after re-introduction of the primarily suspect VMP(s)

User guidance:
'Not applicable' is used when the primarily suspect VMP(s) is not stopped or not re-introduced.

NOTE CONCERNING TRANSMISSION:
LIST: YES, NO, UNKNOWN, NOT APPLICABLE

B.5 Assessment of AE

B.5.1 Attending veterinarian's assessment

User guidance:
Assessment of the attending veterinarian on the association between the VMP(s) and the AE.
Description of the categories in the list is provided in appendix 1.

NOTE CONCERNING TRANSMISSION:
LIST: PROBABLE, POSSIBLE, UNKNOWN, UNLIKELY, NO ATTENDING VET

B.5.2 MAH assessment

User guidance:
Assessment of the MAH on the association between the primarly suspect VMP(s) and the AE.
Description of the categories in the list is provided in appendix 1.

NOTE CONCERNING TRANSMISSION:
LIST: PROBABLE, POSSIBLE, UNKNOWN, UNLIKELY, NO ASSESSMENT

Appendix 1

Reporting veterinarians and the MAH may comment on whether they consider that there is an association between the primarily suspect VMP(s) and the AE reported.
Four categories indicating the assessment of the likelihood of this association can be made.

PROBABLE: for inclusion in the category 'probable', all of the following minimum criteria should be met:

- There should be a reasonable association in time between the administration of the VMP and onset and duration of the reported AE.
- The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the VMP.
- There should be no other equally plausible explanations for the AE.

When any of the above criteria cannot be satisfied (due to lack of sufficient information or conflicting data) then the association cannot be assessed as 'probable'.

POSSIBLE: for inclusion in the category 'possible', association of the AE with administration of the primarily suspect VMP(s) is one of other possible and equally plausible explanations for the described event.

UNLIKELY: where sufficient information exists to establish that the described event was not likely to have been associated with administration of the VMP(s), or other more plausible explanations exist, the assessment should be categorized as 'unlikely'.

UNKNOWN: all events where reliable data is either unavailable or is insufficient to make an assessment should be categorized as 'unknown'.

Appendix 2

To fill an AER related to human exposure to VMP(s), the following user guidance should be considered:

A.3.1: enter the information on the 'attending physician'
A.3.2: if different from animal owner, enter the information on the person exposed to the VMP(s)
B.1: relates to the person exposed to the VMP(s)
B.1.3: select 'human'
B.1.4: not applicable for humans
B.1.5: not applicable for humans
B.1.11: for most cases 'accidental exposure' will be entered
B.2.8: indicate the route of exposure
B.2.9: indicate the dose to which the person was exposed
B.2.10: for most cases 'once' will be entered
B.2.12: for most cases there will be no date entered
B.2.13 ?
B.2.14 ?
B.3.5: not applicable to humans
B.5.1: assessment of attending physician